

Effect of Catatoxic Steroids upon Lidocaine Intoxication

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Abstract—Various steroids have been shown to influence the activity of psychotropic hormones and drugs. Among these, we distinguish “syntoxic” steroids which act by inhibiting excessive reactions to various agents and “catatoxic” steroids which actually destroy certain toxicants and hormones often through the induction of hepatic microsomal enzymes. Thus, the liver can play a decisive role in psychosomatic interrelations by regulating the blood clearance of agents affecting the nervous system. To illustrate these principles, new observations are presented which show that certain catatoxic steroids offer considerable protection against lidocaine, an anesthetic, analgesic drug.

These findings may serve as an example showing how modern research techniques may help us to analyze the possible relationships between the liver and the mind, which were intuitively suspected since Hippocrates created the term “melancholia.”

BY DEFINITION, psychosomatic medicine deals with all interactions between mind and body. The endocrine system has always played a prominent role in this branch of medicine because hormones exert an important effect upon the nervous system and, *vice versa*, nervous stimuli can modify hormone production.

Our own interest in this field has been aroused mainly by the observation that fear, pain and rage are especially strong stressor agents and, hence, readily elicit various manifestations of the general adaptation syndrome, particularly increased secretion of ACTH, corticoids and catecholamines. At the same time, there tends to be a diminution in the productional activity of sex hormones which leads to a decreased libido, menstrual anomalies and, during lactation, diminished milk secretion. These changes have been ascribed to a “shift in pituitary hormone activity” in that, during life-threatening stress, the optimal function of the hypothalamus–anterior pituitary–adrenocortical axis must be assured, even at the cost of reduced elaboration of hormones

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regulating reproduction and other functions of lesser importance for the immediate maintenance of life (Selye, 1950).

All these observations have initiated a great many investigations concerning the action of nervous stimuli (particularly stressors) upon hormone production and, conversely, the effect of endocrine stimuli (particularly steroids) upon the central nervous system.

By 1941, we learned that steroids can not only stimulate emotional reactions (such as euphoria, libido and aggressiveness), but can even produce deep surgical narcosis (Selye, 1941a). This so-called "steroid anesthesia" is greatly prolonged by partial hepatectomy, a fact which suggested that bio-degradation of psychotropic steroids occurs primarily in the liver (Selye, 1941b). Thus, attention was focused on a previously unexplored aspect of psychosomatic interrelations: the role of the liver in the regulation of mental processes. Evidently, in this connection, the rate at which psychotropic hormones are secreted is just as important as the rate of their blood clearance. Subsequent systematic studies showed that, in addition to their direct effects upon the central nervous system, steroids can also influence its function indirectly through their action upon the metabolism of the most diverse natural and artificial compounds which affect the brain and the nerves (Selye, 1971).

During the past few decades it has been confirmed by countless observations that, in addition to their classic functions as regulators of reproduction and general metabolism, steroids also play a decisive role in determining the resistance of the body to many types of stimuli. In this respect, they can be classified according to their mechanism of action into two main groups:

- (A) "Syntoxic" steroids which improve tissue tolerance by permitting a "symbiotic" type of coexistence with the pathogen (*e.g.*, by suppressing non-specific inflammatory or allergic reactions against it).
- (B) "Catatoxic" steroids which actually destroy the aggressor (*e.g.*, through the induction of hepatic microsomal or other enzymes).

The syntoxic effects are virtually limited to glucocorticoids, whereas the catatoxic properties appear to be quite independent of any other known steroid hormone action.

The voluminous literature on the defensive role of hormones has been reviewed recently in an extensive monograph (Selye, 1971). Here, we should only like to report one example illustrating these facts, namely, the influence of catatoxic steroids upon intoxication with lidocaine, an agent possessing strong local and central anesthetic activity.

Materials and Methods

Female ARS/Sprague-Dawley rats (Madison, Wisconsin) with an initial body weight of 100 g (range 90–110 g) were maintained exclusively on Purina Laboratory Chow and tap water, divided into 16 groups, and treated as outlined in Table 1. To obtain the best catatoxic effect, it is important to allow a few days of pre-treatment; hence, all animals received lidocaine (Merck, Sharp and Dohme), 30 mg/100 g body weight in 0.2 ml corn oil sc, once on the fourth day of treatment with the potentially protective substances.

The following steroids were tested for possible protective or sensitizing effects:

PCN [3 β -Hydroxy-20-oxo-5-pregnene-16 α -carbonitrile (Searle)]

CS-1* [9 α -Fluoro-11 β , 17-dihydroxy-3-oxo-4-androstene-17 α propionic acid potassium salt (Searle)]

Ethylestrenol (Organon)

Spironolactone (Searle)

Norbolethone (Wyeth)

Oxandrolone (Searle)

Prednisolone acetate (Roussel)

Triamcinolone (Lederle)

Progesterone (Schering)

Estradiol (Roussel)

Desoxycorticosterone acetate (Schering)

Hydroxydione sodium hemisuccinate (Pfizer)

All steroids were administered at the dose level of 10 mg in 1 ml water (homogenized with a trace of Tween 80), po, twice daily throughout the period of observation.

L-thyroxine (B.D.H.) was injected subcutaneously (in the form of its sodium salt) at the dose of 200 μ g in 0.2 ml water, once daily, and phenobarbital sodium (B.D.H.) and diphenylhydantoin (Eastman) at the dose of 6 mg in 1 ml water, po, twice daily on the same days as the steroids.

Table 1 shows the severity of the anesthesia produced by lidocaine overdosage, estimated 4 hours after injection of the drug, in terms of a scale of: 0 = no change, 1 = just detectable, 2 = mild, and 3 = maximal anesthesia, as described elsewhere (Selye, 1971). For statistical purposes, we recognized only two grades: minor and sometimes dubious degrees of anesthesia (0 to 1 in our scale)

* Catatoxic Steroid Number 1 (manufacturer's code number: SC-11927). The first nonhormonal steroid shown to possess catatoxic activity.

TABLE 1. Effect of Various Agents upon Lidocaine Intoxication

Treatment	Anesthesia (positive/total)
None	13/15
PCN	0/10*
CS-1	2/10*
Ethylestrenol	0/10*
Spironolactone	1/10*
Norbolethone	8/10 NS
Oxandrolone	7/10 NS
Prednisolone-Ac	5/10 NS
Triamcinolone	10/10 NS
Progesterone	9/10 NS
Estradiol	9/10 NS
DOC-Ac	10/10 NS
Hydroxydione	8/10 NS
Thyroxine	9/10 NS
Phenobarbital	8/10 NS
Diphenylhydantoin	10/10 NS

NS = not significant.

* $P < 0.001$.

were rated as negative; all others, as positive. These data were then arranged in a 2×2 contingency table and the statistical significance of the apparent differences between the control and pretreated group computed by the "Exact Probability Test" of Fisher and Yates (Finney, 1948; Siegel, 1956).

Results

As shown by Table 1, the most striking result of this series of experiments was that PCN, CS-1, ethylestrenol and spironolactone give complete, or almost complete, protection against severe lidocaine intoxication. These four steroids are known from previous works (Selye, 1971) to be also the most potent prophylactic agents against a great variety of other drugs. None of the remaining eight steroids tested had a statistically significant protective effect. Thyroxine, phenobarbital and diphenylhydantoin were likewise devoid of prophylactic potency. The inactivity of the latter two drugs is of special interest since they are known to be potent hepatic microsomal enzyme inducers and, in this respect, resemble the catatoxic steroids (Selye, 1971).

At the dose level used, the anesthesia produced by lidocaine was usually very severe. However, only one animal each died in the groups treated with triamcinolone, progesterone, DOC, hydroxydione and thyroxine; hence, under these experimental conditions, a possible protection against the fatal effects of lidocaine intoxication could not have been detected.

Discussion

A search of the earlier literature revealed no data concerning the effects of hormones upon lidocaine intoxication. However, there are some earlier data on endocrine factors affecting resistance to procaine and cocaine. Thus, it has been reported that male rats are more resistant than females to the convulsant action of procaine and that gonadectomy decreases resistance to this drug in males but not in females. Testosterone did not significantly alter resistance to procaine in either sex (Muñoz *et al.*, 1961; Paeile *et al.*, 1964).

More recently, Brodeur *et al.* (1967) noted that the procainesterase activity of the liver is higher in adult male rats than in adult females or immature rats of either sex. Ovariectomy and chronic treatment with testosterone or norethandrolone increased hepatic procainesterase activity in adult females. Conversely, orchidectomy and chronic treatment with estradiol or progesterone decreased this enzyme activity in the livers of adult males. However, immature rats were more resistant to procaine *in vivo* than could be expected from the reduced ability of their livers to hydrolyze procaine *in vitro*. Hence, the authors concluded that "factors other than drug metabolism appear to govern the ultimate toxicity of procaine in immature rats."

Our own earlier experiments in the rat demonstrated that catatoxic steroids (previously shown to protect against numerous other toxicants) effectively combat acute cocaine intoxication. Among these steroids, PCN, ethylestrenol, CS-1 and spironolactone proved to be most effective, but norbolethone, oxandrolone, prednisolone and estradiol likewise offered some protection both against the motor disturbances and the mortality caused by this drug (Selye, *in press*).

The observations reported in this communication confirm for lidocaine the extraordinary protective value of certain catatoxic steroids, namely: PCN, CS-I, ethylestrenol and spironolactone. On the other hand, norbolethone, oxandrolone, estradiol and both glucocorticoids of our series (prednisolone and triamcinolone), which do possess moderate protective activity against cocaine, proved to be ineffective in preventing lidocaine intoxication. These ob-

servations may have some practical importance in protecting patients from the systemic toxicity of lidocaine when the drug is administered topically for the production of local anesthesia. This would be of special importance when regional anesthesia is induced by intravenous injection of lidocaine into an extremity which has been temporarily isolated from the systemic circulation by an arterial tourniquet, a technique recommended by Bell *et al.* (1963).

As stated in the introduction, most of the prophylactic effects of catatoxic steroids have been traced to the induction of drug-metabolizing hepatic microsomal enzymes. It is noteworthy, therefore, that phenobarbital and diphenylhydantoin—known to be very potent inducers of hepatic microsomal enzymes (Selye, 1971)—were unable to protect the rats against lidocaine in the present experiments. It must be assumed, therefore, that either this particular protective action of catatoxic steroids does not depend upon such enzyme induction, or the enzyme activity induced by the steroids differs from that elicited by phenobarbital or diphenylhydantoin pretreatment. It must be kept in mind, however, that mechanisms of drug detoxication are subject to considerable species differences. Thus, in mice, pretreatment with phenobarbital or barbital reduces the toxicity of lidocaine (Heinonen, 1964). On the other hand, in epileptic patients receiving lidocaine intravenously, the rise in plasma lidocaine level proved to be somewhat lower than in control subjects, yet “phenobarbital treatment did not cause further lowering in the plasma lidocaine levels of the epileptics” (Heinonen *et al.*, 1970). In dogs, the blood clearance of iv injected lidocaine was delayed by total hepatectomy, and some delay was also noted in two patients with terminal hepatic cirrhosis (Aldrete *et al.*, 1970). All these observations are consistent with the assumption that despite some species variations, the liver—presumably through its drug-metabolizing enzyme system—plays an important role in the detoxication of lidocaine. In certain species, even the non-steroidal enzyme inducers appear to offer some protection against this drug, but they are less potent than catatoxic steroids and—at least under our experimental conditions—in the rat, phenobarbital and diphenylhydantoin are completely ineffective in this respect.

Extensive metabolic studies would be required to clarify this point, but it is already evident from our findings that virtually complete resistance to near lethal doses of lidocaine can be induced by certain catatoxic steroids in the rat. These observations, as well as the earlier data on the prophylactic value of steroids against cocaine and procaine, are presented primarily to call atten-

tion to a hitherto neglected aspect of psychosomatic medicine, namely the role of defensive hormones as regulators of nervous reactions induced by neuropharmaca. Many of these hormone actions have been shown to result from the induction of defensive hormones in the liver. These findings may serve to analyze, with modern research techniques, the possible relationships between the liver and the mind, which were intuitively suspected ever since Hippocrates created the term "melancholia."

Summary

Earlier data concerning the role of catatoxic and syntoxic steroids in psychosomatic medicine are briefly reviewed. Special attention is called to the fact that many psychotropic hormones and drugs are detoxified by hepatic microsomal enzymes whose activity is enhanced by catatoxic steroids. The resulting acceleration of the blood clearance of hormones and drugs, which influences central nervous activity, is just as important as is the rate of steroid secretion or drug absorption. To illustrate these principles, extensive experiments have been performed to show the protection offered by catatoxic steroids against an anesthetic, analgesic drug.

In rats, pregnenolone-16 α -carbonitrile (PCN), CS-1, ethyl-estrenol and spironolactone proved to be highly potent prophylactic agents against near fatal doses of lidocaine. None of the other steroids, nor thyroxine, phenobarbital or diphenylhydantoin, shared these effects. It is especially noteworthy that here catatoxic steroids differ from nonhormonal inducers of drug-metabolizing microsomes in that only the former protect against lidocaine.

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